FORM-PTO-1390 (Rev. 9-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: 003300-903

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): unassigned 10/048016

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE00/01808	19 September 2000	30 September 1999

TITLE OF INVENTION: VACCINE

APPLICANT(S) FOR DO/EO/US: PER ANTONSSON, KARIN KRISTENSSON, MARIE WALLÉN-ÖHMAN, JOAKIM DILLNER and PETER LANDO

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: A certified copy of Swedish Application No. 9903534-7, filed 30 September 1999, was submitted during the international phase of the examination. Thus the claim for priority has been perfected.

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U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
unassigned 10/048016	PCT/SE00/01808	003300-903

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to U.S. PATENT AND TRADEMARK OFFICE and International Search Report not prepared by the EPO or JPO $1,040.00 (960)		
International preliminary examination fee (37 CFR 1.482) not paid to U.S. PATENT AND TRADEMARK OFFICE but International Search Report prepared by the EPO or JPO $890.00 (970)		
International preliminary examination fee (37 CFR 1.482) not paid to U.S. PATENT AND TRADEMARK OFFICE and international search fee (37 CFR 1.445(a)(2)) paid to U.S. PATENT AND TRADEMARK OFFICE $740.00 (958)		
International preliminary examination fee (37 CFR 1.482) paid to U.S. PATENT AND TRADEMARK OFFICE but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00 (956)		
International preliminary examination fee (37 CFR 1.482) paid to U.S. PATENT AND TRADEMARK OFFICE and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00 (962)		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,040.00	
Surcharge of **$130.00 (154)** for furnishing the oath or declaration later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(e)).	$ --	

Claims	Number Filed	Number Extra	Rate		
Total Claims	28 -20 =	8	X$18.00 (966)	$ 144.00	
Independent Claims	1 -3 =	0	X$84.00 (964)	$ --	
Multiple dependent claim(s) (if applicable)			+$280.00 (968)	$ --	
TOTAL OF ABOVE CALCULATIONS =				$ 1,184.00	
Reduction for ½ for filing by small entity, if applicable (see below).			+	$ --	-
SUBTOTAL =				$ 1,184.00	
Processing fee of **$130.00 (156)** for furnishing the English translation later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$ --	
TOTAL NATIONAL FEE =				$ 1,184.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 (581)** per property			+	$ 40.00	
TOTAL FEES ENCLOSED =				$ 1,224.00	
				Amount to be refunded:	$
				charged:	$

a. ☐ Small entity status is hereby claimed.

b. ☒ A check in the amount of $ 1,224.00 to cover the above fees is enclosed.

c. ☐ Please charge my Deposit Account No. 02-4800 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

d. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4800. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Benton S. Duffett, Jr.
NAME

22,030
REGISTRATION NUMBER

January 28, 2002
DATE

Patent
Attorney's Docket No. 003300-903

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
PER ANTONSSON et al.	)	**BOX PCT**
	)	
Application No.: (unassigned)	)	Attention: DO/EO/US
	)	
Filed: January 28, 2002	)	Group Art Unit: (unassigned)
	)	
For: VACCINE	)	Examiner: (unassigned)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a national phase filing of International Application No. PCT/SE00/01808, filed September 19, 2000.

Please amend the Application as indicated.

IN THE ABSTRACT:

Please add the Abstract of the Disclosure that is provided on a separate sheet.

IN THE CLAIMS:

Kindly replace Claims 9, 13, 16, 18, 19, 21, 23 and 25 as follows:

9. (Amended) A carrier according to claim 6, capable of giving rise to a protective antibody response.

13. (Amended) A carrier according to claim 1 in combination with a minor capsid protein L2 of human papillomavirus (HPV-L2 protein).

16. (Amended) A carrier according to claim 1 in which said substance is an oligo- or polynucleotide.

18. (Amended) A vaccine, comprising as an active ingredient a carrier as defined in claim 1.

19. (Amended) A polynucleotide coding for the carrier as defined in claim 1.

21. (Amended) A method of preventing or treating viral, bacterial or parasite infections by vaccination with a carrier as defined in claim 1.

23. (Amended) A method of preventing or treating development of benign or malign consequences of human papillomavirus infection by vaccination with a carrier as defined in claim 1.

25. (Amended) A method of preventing or treating cancer by vaccination with a carrier as defined in claim 1.

Please add the following new Claims 27 to 28:

27. (New) A carrier according to claim 7, capable of giving rise to a protective antibody response.

28. (New) A carrier according to claim 8, capable of giving rise to a protective antibody response.

REMARKS

The present Amendment adds on Abstract of the Disclosure on a separate sheet and modifies the claim format only so as to eliminate the use of multiple dependency.

An Information Disclosure Statement is being filed herewith.

The examination and allowance of the Application are respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

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Date: January 28, 2002

Attachment to Preliminary Amendment dated January 28, 2002

Abstract of the Disclosure

The invention relates to a carrier for introduction of a substance into cells, comprising a major capsid protein L1 of human papillomavirus (HPV-L1 protein) which has been intentionally modified to remove type-specific epitope(s) causing production of neutralising antibodies. The invention also includes an oligo- or polynucleotide coding for said carrier, vaccines comprising said carrier or said oligo- or polynucleotide, as well as methods of using the carrier or the oligo- or polynucleotide in vaccination against infections of human papillomavirus, or against development of consequences of such an infection, or against development of certain cancers.

Attachment to Preliminary Amendment dated January 28, 2002

Marked-up Claims 9, 13, 16, 18, 19, 21, 23 and 25

9. (Amended) A carrier according [any one of claims 6-8] to claim 6, capable of giving rise to a protective antibody response.

13. (Amended) A carrier according to [any one of claims 1-12] claim 1 in combination with a minor capsid protein L2 of human papillomavirus (HPV-L2 protein).

16. (Amended) A carrier according to [any one of claims 1-15] claim 1 in which said substance is an oligo- or polynucleotide.

18. (Amended) A vaccine, comprising as an active ingredient a carrier as defined in [any one of claims 1-17] claim 1.

19. (Amended) A polynucleotide coding for the carrier as defined in [any one of claims 1-17] claim 1.

21. (Amended) A method of preventing or treating viral, bacterial or parasite infections by vaccination with a carrier as defined in [any one of claims 1-17] claim 1.

Attachment to Preliminary Amendment dated January 28, 2002

Marked-up Claims 9, 13, 16, 18, 19, 21, 23 and 25

23. (Amended) A method of preventing or treating development of benign or malign consequences of human papillomavirus infection by vaccination with a carrier as defined in [any one of claims 1-17] claim 1.

25. (Amended) A method of preventing or treating cancer by vaccination with a carrier as defined in [any one of claims 1-17] claim 1.

VACCINE

FIELD OF THE INVENTION

The present invention relates to a carrier for introduction of substances into cells comprising a modified major capsid protein L1 of human papillomavirus (HPV-L1 protein) devoid of type-specific epitopes causing production of neutralising antibodies. The invention also includes an oligo- or polynucleotide coding for said carrier, vaccines comprising said carrier or said oligo- or polynucleotide, as well as methods of using the carrier or the oligo- or polynucleotide in vaccination against viral, bacterial or parasite infections as well as against development of certain cancers. Especially, infections of human papillomavirus and the development of cancer as a consequence of such infections are recognised.

BACKGROUND OF THE INVENTION

The Human Papillomavirus (HPV) is since long established as the major cause of cervical cancer (1), and has in recent years also been established as a cause of cancers of the penis, vulva, vagina, anus and orofarynx. There also exists indications that the virus may be involved in some cancers of the prostate, esophagus and in other head and neck cancers. HPV vaccine development is therefore a prime priority of preventive cancer research today (2).

The HPVs exist as >100 different types. Although types are defined by genetic homology, the genotypes have hitherto shown a strikingly good concordance with serotypes, i.e. hyperimmune antisera against one type will only neutralise the same type and not other genotypes. Cross-neutralisations have only been reported for certain closely related types and have had titers 2 orders of magnitude less than for the type-specific neutralisation (2,3).

The HPV capsid consists of 72 capsomers each containing 5 copies of the HPV major capsid protein L1. A minor capsid protein, L2, is present in much smaller amounts in the capsid (1:12 compared to the L1 protein) and the location of L2 is uncertain (2).

A number of small viruses express capsid proteins that when expressed self-assemble to form virus-like particles (VLPs) (i.e. particles morphologically similar to virus particles, but lacking the viral genome). The HPV major capsid protein L1 is among the best studied (2). HPV VLPs containing only L1 are morphologically similar to VLPs containing both L1 and L2 (2). Both particles with L1 only and particles with L1/L2 are highly efficient in eliciting a high-titered neutralising antibody response in several animal model systems (rabbits, cows, dogs and rhesus monkeys), even when injected in the absence of adjuvant (2).

Vaccination with papillomavirus VLPs has been shown to be highly efficient for protection, mediated by neutralising antibodies, against subsequent challenge with both cutaneous and mucosal papillomaviruses, but only in a type-specific manner (2). This strong type-specificity is surprising, since the major capsid protein of the HPVs is a highly evolutionarily conserved protein with very few amino acid changes between genetically related, but not cross-neutralising, HPV types.

The most common oncogenic HPVs are HPV16, 18, 31 and 45. HPV16 is found in about 50% of cervical cancers, HPV18 in about 20%, and these four types together correspond to >80% of all cervical cancers. Therefore, a commonly contemplated strategy is to manufacture vaccines containing HPV capsids of the 4 most common HPV types together (2).

Albeit this strategy appears likely to work for achieving significant cancer reduction, it has some distinct disadvantages. The formulation of vaccines containing 4 active components mixed together involves a

substantial additional cost in manufacturing and efficacy testing and quality control of each component.

Furthermore, some 10-20% of cervical cancers are caused by HPV types not included in the presently manufactured vaccine candidates. Apart from the fact that the vaccine could not possibly protect against these types, the possibility also exists that elimination of the 4 most common oncogenic HPV types may cause an increase in the prevalence of the other oncogenic HPV types, thus further diminishing the cancer-preventive gains. This latter scenario is, as predicted from population biology studies, likely to follow if there exists interference between different viral types. Several lines of indirect evidence do indicate that interference between HPV types does exist.

Several other HPV types cause significant morbidity and mortality, most notably HPV 6 and 11 that cause genital condylomas and recurrent respiratory papillomatoses, and HPVs 5 and 8 that cause cutaneous skin-cancers in the immunosuppressed host. In spite of the obvious advantages of broadly cross-reactive vaccines, the possibility to generate a broadly cross-reactive vaccine, by modifying the L1 protein to not contain immunodominant type-specific epitopes, has not been proposed. Several surface exposed and cross-reactive epitopes are exposed on papillomavirus particles (WO 96/33737), but are not immunogenic in the presence of the immunodominant type-specific epitope (4). Therefore, by modifying the L1 to remove immunodominant type-specific epitopes, it should be possible to generate a cross-reactive papillomavirus vaccine, using a modified HPV-L1 protein as a carrier of surface exposed HPV derived antibody epitopes.

Furthermore, VLPs are highly efficient in eliciting a cytotoxic T lymphocyte (CTL) response, and VLP vaccines have been reported to be highly efficacious (through a CD8+cell-dependent mechanism) in preventing and treating transplantable cancers in several mouse models, in spite

of the fact that immunization is made with an exogenous protein (5). The high immunogenicity appears to be due in part to the preservation of an active mechanism for infection of the cell (designated pseudo-infection, as no viral genome is introduced) which results in the capsid protein being processed and presented in the MHC class I presentation pathway (6). VLPs are therefore of general interest from a vaccine biotechnology point of view, since they can be used as a vehicle for efficient immunogenic delivery of any antigen (7).

Efficient immunisation using wild-type HPV VLPs carrying foreign antigens has been demonstrated in several systems, e.g. the MAGE melanoma antigens and human immunodeficiency virus antigens.

A potential problem using VPLs as vehicles for immunogenic delivery is blocking by type-specific neutralising antibodies. In Sweden 16% of the adult population are sero-positive for HPV-16, reflecting the importance of the problem. In addition, therapeutic vaccination is expected to require recurrent treatments, likely to induce a type-specific antibody response towards a wild-type VLP carrier.

Therefore, by modifying the L1 protein to remove type-specific epitopes causing production of neutralising antibodies, as has been described (8), and introduce antibody or T-cell epitopes in this carrier, it should be possible to generate an immunological response towards the introduced peptide, without obstruction from type-specific neutralising antibodies directed towards the carrier itself.

SUMMARY OF THE INVENTION

An object of the present invention is to provide means for preventing and treating viral, bacterial or parasite infections, especially of human papilloma virus, and the development of benign or malign consequences of such infections, as well as means for treating and preventing cancer.

The present invention provides for the use of a modified HPV-L1 protein devoid of type-specific epitopes causing production of neutralising antibodies, as a carrier of a substance into cells. As a result of the modification, this HPV-L1 protein carrier does not induce production of overt neutralising antibodies towards the carrier itself. In an embodiment of the invention, one or more amino acids may be deleted from said protein.

In particular, the invention provides for such an HPV-L1 protein in fusion with a peptide.

The invention also provides for such a carrier which is capable of giving rise to a protective antibody response, which antibody response may be cross-reactive towards two or more serologically defined subtypes of human papillomavirus.

The carrier must be physically coupled, that is fused, to the peptide for which it acts as a carrier, thus creating a fusion protein.

Particularly, peptides derived from HPV proteins and defining linear antibody epitopes and T-cell epitopes are recognised.

There is also envisaged combinations of said carrier with a minor coat protein of human papillomavirus (HPV-L2 protein), native or modified. Also this HPV-L2 protein can itself be fused to one or more further peptides.

The invention also provides for an oligo- or polynucleotide coding for said carrier. The invention makes it possible to create a better basis for eliciting an MHC class I mediated response, i.e. creating cytotoxic T-cells, without giving rise to type-specific neutralising antibodies towards the carrier, or without type-specific neutralising antibodies being present at the start.

It is also possible to use an HPV-L1 protein, modified as described above, as a carrier of oligo- or polynucleotides to cells.

DETAILED DESCRIPTION OF THE INVENTION

In one of its aspect, the invention provides for a carrier for introduction of a substance into cells, comprising a major capsid protein L1 of human papillomavirus (HPV-L1 protein) which has been intentionally modified to remove type-specific epitope(s) causing production of neutralising antibodies. In one preferred embodiment said HPV-L1 protein is in fusion with a peptide.

Preferably, said peptide comprises one or more T-cell epitopes, especially such epitopes derived from tumor, bacterial, parasite, viral or auto-antigens. In another preferred embodiment, said peptide comprises one or more antibody epitopes, such as tumor, bacterial, parasite, viral or auto-antigens, especially papillomavirus antigens.

The carrier can also be combined with a minor capsid protein L2 of human papillomavirus (HPV-L2 protein), which in its turn may be fused to one or more further peptides. These further peptides are e.g. T-cell or antibody epitopes, which may be derived from tumor, bacterial, parasite, viral or auto-antigens.

In a further embodiment the fusion protein is used as a carrier of oligo- or polynucleotides, e.g. such oligo- or polynucleotides which are coding for an antigen or an immunostimulatory (poly)peptide.

In another aspect, the invention provides for an oligo- or polynucleotide coding for the carrier as defined.

In further aspects, the invention provides for vaccines, comprising as an active ingredient a carrier or an oligo- or polynucleotide as defined above.

In further aspects of the invention there is provided methods of preventing or treating viral, bacterial or parasite infections by vaccination with a carrier or an oligo- or polynucleotide as defined above. In a preferred embodiment the infections is caused by papillo-

mavirus.

There is also provided methods of preventing or treating development of benign or malign consequences of human papillomavirus infection by vaccination with a fusion protein or an oligo- or polynucleotide as defined above.

In embodiments of the methods said human papillomavirus infection is warts or laryngeal papillomatosis.

Further aspects of the invention comprise methods of preventing or treating of cancer, including cancer of cervix, penis, vulva, vagina, anus and orofarynx, by vaccination with a fusion protein or an oligo- or polynucleotide as defined above.

REFERENCES

- 1. H. zur Hausen. Viruses in human cancers. Science 1991; 254: 1167-1173.

- 2. D. R. Lowy and J. T. Schiller. Papillomaviruses and cervical cancer: Pathogenesis and vaccine development. J. Natl. Cancer Inst. Monographs 1998; 23: 27-30.

- 3. W. I. White, S. D. Wilson, W. Bonnez, R. C. Rose, S. Koenig and J. A. Suzich. In vitro infection and type-restricted antibody-mediated neutralization of authentic human papillomavirus type 16. J. Virol. 1998; 72: 959-964.

- 4. H. L. Greenstone, J. D. Nieland, K. E. deVisser, M. E. De Bruijn, R. Kirnbauer, R. B. Roden, D. R. Lowy, W. M. Kast and J. T. Schiller. Chimeric papillomavirus virus-like particles elicit antitumor immunity against the E7 oncoprotein in an HPV16 tumor model. Proc. Natl. Acad. Sci. USA 1998; 95: 1800-1805.

- 5. S. Peng, I. H. Frazer, G. J. Fernando and J. Zhou. Papillomavirus virus-like particles can deliver defined CTL epitopes to the MHC class I pathway. Virology 1998; 240: 147-157.

- 6. M. Muller, J. Zhou, T. D. Reed, C. Rittmuller, A. Burger, J. Gabelsberger, J. Braspenning and L. Gissmann. Chimeric papillomavirus-like particles. Virology 1997; 234: 93-111.

- 7. White, W.I., Wilson, S.D., Palmer-Hill, F.J., Woods, R.M., Ghim, S.-J., Hewitt, L.A., Goldman, D.M., Burke, S.J., Jenson, A.B., Koenig, S. and Suzich, J.A.: Characterization of a Major Neutralizing Epitope on Human Papillomavirus Type 16 L1. Virology, 1999; 73:4882-4889.

- 8. Wang, Z., Christensen, N.D., Schiller, J.T. and Dillner, J.: A monoclonal antibody against intact Human Papillomavirus type 16 capsids blocks the serological reactivity of most human sera. J. Gen. Virol., 78, 2209-2215 (1997).

CLAIMS

1. A carrier for introduction of a substance into cells, comprising a major capsid protein L1 of human papillomavirus (HPV-L1 protein) which has been intentionally modified to remove major type-specific epitope(s) causing production of neutralising antibodies.

2. A carrier according to claim 1, wherein one or more amino acids have been deleted.

3. A carrier according to claim 1, wherein said HPV-L1 protein is in fusion with a peptide.

4. A carrier according to claim 3, wherein said peptide comprises one or more T-cell epitopes.

5. A carrier according to claim 4, wherein said one or more T-cell epitopes are derived from a group of antigens comprising tumor, bacterial, parasite, viral or auto-antigens.

6. A carrier according to claim 3, wherein said peptide comprises one or more antibody epitopes.

7. A carrier according to claim 6, wherein said one or more antibody epitopes are derived from a group of antigens comprising tumor, bacterial, parasite, viral or auto-antigens.

8. A carrier according to claim 7, wherein said one or more antibody epitopes are derived from human papillomavirus antigens.

9. A carrier according any one of claims 6-8, capable of giving rise to a protective antibody response.

10. A carrier according to claim 9, wherein said protective antibody response is cross-reactive towards two or more serologically defined subtypes of human papillomaviruses.

11. A carrier according to claim 10, wherein said protective respones is raised against two or more of the group comprising HPV-L1 proteins derived from human papillomavirus implicated in tumor induction.

12. A carrier according to claim 11, wherein said protective antibody response is cross-reactive towards two or more of the group of HPV-L1 proteins comprising L1 proteins of HPV-16, HPV-18, HPV-31 and HPV-45.

13. A carrier according to any one of claims 1-12 in combination with a minor capsid protein L2 of human papillomavirus (HPV-L2 protein).

14. A carrier according to claim 13, wherein said HPV-L2 protein is in fusion with one or more further peptides.

15. A carrier according to claim 14, wherein said one or more further peptides are chosen from a group of antigens comprising tumor, bacterial, parasite, viral and auto-antigens.

16. A carrier according to any one of claims 1-15, in which said substance is an oligo- or polynucleotide.

17. A carrier according to claim 16, whereby said oligo- or polynucleotide is coding for one or more antigens or immunostimulatory (poly)peptides.

18. A vaccine, comprising as an active ingredient a carrier as defined in any one of claims 1-17.

19. A polynucleotide coding for the carrier as defined in any one of claims 1-17.

20. A vaccine, comprising as an active ingredient a polynucleotide as defined in claim 19.

21. A method of preventing or treating viral, bacterial or parasite infections by vaccination with a carrier as defined in any one of claims 1-17.

22. A method according claim 21 of preventing or treating infection of human papillomavirus.

23. A method of preventing or treating development of benign or malign consequences of human papillomavirus infection by vaccination with a carrier as defined in any one of claims 1-17.

24. A method according to claim 23, whereby said human papillomavirus infection is chosen from the group comprising warts and laryngeal papillomatosis.

25. A method of preventing or treating cancer by vaccination with a carrier as defined in any one of claims 1-17.

26. A method according to claim 25, whereby said cancer is chosen from the group comprising cancer of cervix, penis, vulva, vagina, anus and orofarynx.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to Provisional and International (PCT) Applications)

Attorney's Docket No. 003300-903

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (IF ONLY ONE NAME IS LISTED BELOW) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (IF PLURAL NAMES ARE LISTED BELOW) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION ENTITLED:

VACCINE

The specification of which (check only one item below):

- ☐ is attached hereto.
- ☐ was filed as United States Patent Application Number _____
  on _____
  and was amended on _____ (if applicable).
- ☐ was filed as International (PCT) Application Number _____
  on _____
  and was amended on _____ (if applicable).

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I ACKNOWLEDGE THE DUTY TO DISCLOSE TO THE U.S. PATENT AND TRADEMARK OFFICE ALL INFORMATION KNOWN TO ME TO BE MATERIAL TO PATENTABILITY AS DEFINED IN TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (as amended effective March 16, 1992);

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than six months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code, §§ 119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any International (PCT) Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International (PCT) Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
Sweden	9903534-7	30 September 1999	☒Yes ☐No
			☐Yes ☐No
			☐Yes ☐No
			☐Yes ☐No
			☐Yes ☐No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

_____ _____
(APPLICATION NUMBER) (FILING DATE)

_____ _____
(APPLICATION NUMBER) (FILING DATE)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and International (PCT) Applications)

Attorney's Docket No. 003300-903

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States applications(s) or International (PCT) Application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations § 1.56, which became available between the filing date of the prior application(s) and the national or international filing date of this application:

PRIOR U.S. APPLICATIONS OR INTERNATIONAL (PCT) APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. § 120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
		☐	☐	☐

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)			
SE00/01808	19 September 2000				

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the U.S. Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and International (PCT) Applications)

Attorney's Docket No. 003300-903

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